REMARKS

Claims 21 and 23 are pending in the application, with Claims 27-37 being withdrawn from consideration pursuant to restriction requirement. Claims 21 and 23 stand rejected. Claim 21 is hereby amended, with support for said amendments being found generally throughout the specification and specifically within Claim 22 and pages 2 and 15-17 of the specification (see for instance "Activity assay and inhibition of PDE activity" on page 16). Claims 21 and 23, as amended, thus now stand pending.

Applicants wish to thank the Examiner for the withdrawal of the 112, Second Paragraph rejection and the withdrawal of the Gretarsdottir 103(a) reference. The only rejection of record pursuant to the Advisory Action of April 17, 2008 is the Frenette 103(a) rejection.

Claim Rejections

1. 35 USC § 103(a)

A) Claims 21 and 23 remain rejected under 35 USC 103(a) as being unpatentable over Frenette (WO 00/64874). The Examiner has alleged Frenette teaches the existence of multiple PDE4's , but acknowledges that Frenette does not teach any specific isoforms of PDE4 much less obtaining/determining inhibitors which are selective for specific individual isoforms of PDE4. Frenette is also alleged to disclose treatment of a laundry list of 25 or so diseases with compounds that are selective and potent inhibitors of PDE4. The last two diseases to which the compounds of Frenette "may be put include" arterial sclerosis/atherosclerosis (pg 11). The Examiner acknowledges that Frenette does not teach screening and identifying modulators of PDE4D. Applicants respectfully traverse and overcome said rejection.

First, and contrary to the Examiner's assertion, Frenette at best discloses inhibitors of PDE4 enzymes, but does not disclose activity of the PDE4 enzymes themselves with the development of any diseases, much less atherosclerosis or

stenosis. Frenette does not disclose, teach or otherwise suggest step 1 of Claim 21 (measuring activity of a PDE4 target), nor does Frenette disclose, teach or otherwise step 2 of Claim 21 (administering a compound suspected to be an activator or inhibitor of PDE4 to the PDE4 target). Therefore at least two steps of Applicants claimed invention are not disclosed, taught or even suggested by Frenette. One of ordinary skill in the art arguably would not have even considered Frenette, given that Frenette seemingly does not contain any data showing a connection between PDE4 activity and the development of restenosis or atherosclerosis, respectively.

Second, Frenette does not disclose, teach nor suggest any specific isoforms of PDE4, much less the specific isoforms of PDE4 of the claimed invention. Thus, all the specific PDE4 isoforms of Claim 1 are not disclosed, taught or even suggested by Frenette. Therefore, arguably all steps of Applicants claimed invention are not disclosed, taught or even suggested by Frenette. One of ordinary skill in the art arguably would not have even considered Frenette, given that Frenette seemingly does not contain any data showing a connection between PDE4 activity and the development of restenosis or atherosclerosis, respectively.

Third, there is no enablement anywhere in Frenette supporting the alleged laundry list of uses to which the Frenette compounds "may be put" in lines 14-22 on page 11. Applicants submit that Frenette at best only enables inflammation of the lung. There are no examples nor data nor experimentation which supports the Frenette compounds being used for restenosis or atherosclerosis. Absent enablement, Applicants submit that Frenette et al would not be considered by one of ordinary skill of the art as teaching or suggesting or motivating one of ordinary skill in the art with regard to the method of Applicants' Claim 1. Absent enablement, Applicants respectfully submit that Frenette is not proper 103(a) art.

The lack of teaching, suggestion or motivation in Frenette for atherosclerosis or restenosis is clear to one of ordinary skill in the art. Frenette et al (WO 00/64874)

relates to heterosubstituted pyridines derivatives that are inhibitors of PDE4 at concentrations at which they have little or no inhibitory action on other PDE isoenzymes. These compounds inhibit the human recombinant PDE4 enzyme and also elevate cAMP in isolated leukocytes. The compounds thus prevent, alleviate or reduce inflammation in the lungs, such as that induced by carrageenan, platelet-activating factor (PAF), interleukin-5 or antigen challenge. The compounds also suppress the hyperresponsiveness of airway smooth muscle seen in inflamed lungs (WO 00/064874, p. 2, lines 25 - 32). According to p. 3, first paragraph the compounds are of use in medicine, especially in the prophylaxis and treatment of asthma.

Thus, the focus of WO 00/64874 is on compounds having anti-inflammatory activities. This is further underlined by the assays for determining the biological activity of the inventive compounds (see p. 38 - 40). Assay 1:"LPS and FMLP induced TNF alpha and LTB4 assay in human whole blood" is an assay for testing the anti-inflammatory activity of compounds. The second assay "Anti-allergic activity in vivo" tests the effect of the compounds on an IgE mediated allergic pulmonary inflammation induced by inhalation of antigen by sensitized guinea pigs. Therefore, at best, the only determined activities of the inventive compounds would allegedly be their anti-inflammatory and anti-allergic activity.

WO 00/64874 at best discloses compounds having anti-inflammatory and/or anti-allergic activity. It does not disclose a compound having anti-atherosclerotic activity. It does not support or disclose any data for anti-atherosclerotic activity. A mere listing of possible diseases that might be treatable by the inventive compounds without support of in vitro data is not an enabling teaching for a person skilled in the art. WO does not enable the laundry list of possible diseases in line 14-22 on page 11, much less enable a treatment of atherosclerosis.

Applicants therefore respectfully submit that Frenette lacks support for treating arterial restenosis and atherosclerosis as Frenette lacks any in vitro or in vivo biological

activity data showing that the inventive compounds could be used for the treatment of arterial restenosis and atherosclerosis. In other words, Frenette is not enabling with respect to the use of the inventive compounds for the treatment of arterial restenosis and atherosclerosis.

Fourth and finally, Frenette, as a non-enabling reference with respect to the use of the inventive compounds for the treatment of arterial restenosis and atherosclerosis, does not present a specific finite and small number of identified, predictable solutions that would convince an ordinary skilled artisan of obviousness. Unlike the situation in *KSR International Co. v Teleflex Inc*, 127 S. Ct. 1727 (2007), Frenette speaks in generalities, without evidentiary support. The rationale in KSR presumes evidentiary support and indeed enablement. As the Fed Circuit has recognized in *Ortho-McNeil Pharmaceuticals v Mylan Laboratories*, 2007-1223 (Fed Cir. March 31, 2008), the instant case "is not the easily traversed, small and finite number of alternatives that KSR suggested might support an inference of obviousness" (Slip op pages 9-10).

Thus, Frenette does not suggest nor disclose, nor generally teach, the specific claimed isoforms of PDE4 of Claim 1, much less enable the use of said claimed isoforms for the treatment of arterial restenosis and atherosclerosis. One of ordinary skill in the art would not rely upon such an non-enabled reference, especially given the lack of any data showing a connection between PDE4 activity and the development of restenosis or atherosclerosis.

Therefore, Applicants respectfully submit that WO 00/64874 lacks an enabling teaching with regard to PDE4 inhibitors for the treatment of arterial restenosis and atherosclerosis and is thus not applicable as 103(a) art as to the claimed invention.

In conclusion, Applicants respectfully submit that Frenette does not teach, disclose nor suggest at least two steps of Applicants' claimed invention, nor the specific claimed isoforms utilized in said invention and that accordingly Claims 21 and 23, as

amended, are novel and non-obvious. Furthermore Applicants submit that Frenette is not an enabling disclosure with regard to PDE4 inhibitors for the treatment of arterial restenosis and atherosclerosis. Applicants therefore respectfully request that the 103(a) rejection be withdrawn and that Claims 21 and 23, as herein amended, be put into condition for allowance.

No further fee is required in connection the filing of this Amendment. If any additional fees are deemed necessary, authorization is given to charge the amount of any such fee to Deposit Account No. 08-2525.

Respectfully submitted,

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